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Abstract: Patients on levodopa therapy frequently require additional antipsychotic pharmacotherapy. However, consideration must be given to antagonistic interactions on dopamine receptors between levodopa and antipsychotics, and efficacy and safety of such combinations. We therefore aimed to explore the practice and rationale of coprescription between levodopa and antipsychotics in psychiatric patients.A descriptive retrospective study based on cross-sectional prescription data repeatedly collected from psychiatric inpatients through the international Drug Safety in Psychiatry (AMSP) program between 1994 and 2008 was undertaken.Within a population of 84 596 psychiatric patients the prevalence of levodopa therapy was 1.0% (n=886). Among those patients on levodopa therapy 59.6% (n=528) also received antipsychotics. Quetiapine coprescription increased after its first marketing in 2000 to 45.9% in 2008. Coprescription of clozapine and olanzapine decreased from up to 25 and 22%, respectively, before to less than 10% after the introduction of quetiapine. Coprescribing of other antipsychotics remained approximately stable with average prevalences between 6 and less than 1%.Quetiapine has now replaced clozapine as the most frequently coprescribed neuroleptic in psychiatric patients with levodopa therapy. This is in accordance with recent data indicating a low potential for clinically relevant interactions with levodopa and efficacy against psychosis in levodopa-treated patients. The combined use of antipsychotics other than quetiapine and clozapine with levodopa is less common and generally not supported by appropriate evidence.

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Coprescribing of Levodopa with Antipsychotics in a Population of 84,596 Psychiatric Inpatients from 1994 to 2008

Patrick Haueis[1], Stefan Russmann[1,2], Olesya I. Zorina[1], Renate Grohmann[3], Gerd A. Kullak-Ublick[1,2], Eveline Jaquenoud Sirot[4], Heike Russmann[5]

[1] Department of Clinical Pharmacology and Toxicology, University Hospital Zurich, Zurich, Switzerland

[2] Zurich Center for Integrative Human Physiology (ZIHP), Zurich, Switzerland

[3] Department of Psychiatry, Ludwig Maximilian University, Munich, Germany

[4] Psychiatric Services Aargau, Aargau, Switzerland

[5] Department of General and Social Psychiatry, Psychiatric University Hospital Zurich

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Correspondence:
Stefan Russmann, MD
Department of Clinical Pharmacology and Toxicology, University Hospital Zurich
Rämistrasse 100, 8091 Zurich, Switzerland
phone: +41 44 255 20 67
fax: +41 44 255 44 11
e-mail: stefan.russmann@usz.ch

ABSTRACT

Introduction Patients with levodopa therapy frequently require additional antipsychotic pharmacotherapy. However, consideration must be given to antagonistic interactions on dopamine receptors between levodopa and antipsychotics, and efficacy and safety of such combinations. We therefore aimed to explore the practice and rationale of coprescription between levodopa and antipsychotics in psychiatric patients.

Methods Descriptive retrospective study based on cross-sectional prescription data repeatedly collected from psychiatric inpatients through the international Drug Safety in Psychiatry (AMSP) program between 1994 and 2008.

Results Within a population of 84,596 psychiatric patients the prevalence of levodopa therapy was 1.0% (n=886). Among those patients with levodopa therapy 59.6% (n=528) also received antipsychotics. Quetiapine coprescription increased after its first marketing in 2000 to 45.9% in 2008. Coprescription of clozapine and olanzapine decreased from up to 25 and 22%, respectively, before to less than 10% after introduction of quetiapine. Coprescribing of other antipsychotics remained approximately stable with average prevalences between 6 and less than 1%.

Discussion Quetiapine has now replaced clozapine as the most frequently coprescribed neuroleptic in psychiatric patients with levodopa therapy. This is in accordance with recent data indicating a low potential for clincially relevant interactions with levodopa and efficacy against psychosis in levodopa-treated patients. The combined use of other antipsychotics than quetiapine and clozapine with levodopa is less common and generally not supported by appropriate evidence.

Keywords Antipsychotics, drug interactions, levodopa, Parkinsons's disease, restless legs syndrome, pharmacoepidemiology

INTRODUCTION

Levodopa is indicated for the treatment of idiopathic Parkinson's disease (PD), Parkinson syndromes, and restless legs syndrome (RLS), but not for drug-induced extrapyramidal symptoms (EPS). PD is associated with psychosis with an estimated incidence rate of 79.7 per 1000 person-years [1], and central dopaminergic overactivity as well as an imbalance in the cholinergic neurotransmission play a key role in the underlying pathophysiology [2, 3]. On the one hand PD itself is associated with psychosis [4]. But more importantly, in the majority of PD patients psychosis is actually precipitated by dopaminergic treatment for PD, including levodopa [1, 5, 6]. Similarly, the dopamine system is also involved in the pathophysiology of RLS [7], which is the foundation for its treatment with dopaminergic drugs including levodopa. In analogy to PD dopaminergic treatment for RLS is also associated with psychotic disorders [8]. Therefore, in order to control psychotic symptoms in levodopa-treated patients neurologists and psychiatrists frequently combine levodopa with antipsychotics in clinical practice.

In a previous study we investigated the prevalences of interacting drug combinations in a large population of psychiatric inpatients collected through the international Drug Safety in Psychiatry (AMSP) program, but our analyses did not yet include detailed studies of drug interactions between selected drug classes of interest [9]. The current study aimed to explore the combined use of levodopa and antipsychotics in a large representative psychiatric inpatient population that reflects prescribing behavior in clinical practice over time.

METHODS

Data Source

AMSP is an ongoing international multicenter drug safety program that has been collecting data on pharmacotherapy and adverse drug events from psychiatric hospitals in a naturalistic setting since 1993. Its methods have been described in detail elsewhere [10, 11]. Briefly, AMSP consists of two principle data collections from more than 80 hospitals in Germany, Switzerland and Austria, and more recently also from one hospital each in Belgium and Hungary. First, in a cross-sectional approach all participating hospitals survey psychiatric inpatients on two reference days per year. All drugs administered on these days are recorded along with the patients' age, gender and leading psychiatric diagnoses. Second, severe adverse drug events that occur at these hospitals during psychopharmacological drug treatment are continuously reported and collected. For the current study we used only the cross-sectional AMSP prescription dataset.

Study population and design

Selection of the study population and data management have been described in detail in our previous study [9]. Briefly, we received an anonymized dataset that had been extracted from the AMSP database and contained all cross-sectional data collected from the AMSP program between 1994 and 2008. Subsequently we executed extensive reformatting, quality controls and matching of ATC codes to all prescribed active substances. Compared to our previous study another 11 patients were excluded for the current analysis because the date of data collection was not specified, and this would have interfered with time trend analyses. Within the resulting population of 84,567 patients we identified all patients with prescriptions for levodopa and recorded

all concomitant prescriptions at the day of prescription data collection. The ethics committee of the Ludwig Maximilian University Munich, the location of the AMSP main data center, had approved the study with a waiver of authorization.

Data analysis

Data analysis was primarily descriptive with presentation of results in tables and graphs as appropriate. The chi-square test was used for comparing changes in the proportion of patients with prescriptions of specific drugs over two different time strata. Alternatively, we fitted changes over several calendar years to a simple linear regression model. Data management, analyses, tables and graphs were done using STATA Version 11.2 for MacOS X (STATA Corporation, College Station, TX, USA) and SPSS Version 18 for MacOS X (IBM Corporation, Somers, NY, USA).

RESULTS

Characteristics and overall pharmacotherapy of patients with levodopa therapy

Among 84,567 psychiatric inpatients we identified 886 patients with a prescription of levodopa. Looking at time trends for levodopa use in the source population we found that the proportion of patients with levodopa prescriptions increased by 29% from 0.9% to 1.2% ($p<0.005$) comparing the time strata from 1994-2002 vs. 2003-2008, and we also noticed a trend towards a continuous increase over time by calendar years (linear regression: $R^2=0.49$, $p=0.004$). This increase may at least partially be attributable to an increasing number of gerontopsychiatric wards that contributed to data collection in the source population over time. Characteristics of patients with levodopa treatment are presented in **Table 1**. Of note, available ICD-10 diagnoses are

primary psychiatric admission diagnoses that are reliably captured in the database along with all prescribed drugs, whereas reliable information regarding the indication or dose of pharmacotherapy was not available. Most frequently coprescribed drug classes are presented in **Table 2**, showing that antipsychotics, antidepressants and anxiolytics are the top three coprescribed drug classes in psychiatric patients with levodopa therapy. Therapy with other dopaminergic drugs in addition to levodopa is presented in **Table 3**. Among all 886 patients with levodopa therapy 239 (27.0%) had at least one additional dopaminergic drug that is typically combined with levodopa for the treatment of PD or Parkinson syndrome and therefore strongly suggest those as the underlying indication. The remaining 647 (73.0%) patients had dopaminergic monotherapy with levodopa, compatible with either PD, Parkinson syndrome or restless legs syndrome as the most likely indication.

Coprescribing of levodopa and antipsychotics

Combined use of levodopa and antipsychotics is presented in **Table 4** and **Figure 1**. Clozapine use showed a moderate decrease in an approximately linear fashion between 1996 and 2008 (linear regression analysis: R^2=0.51, p=0.006). However, the most prominent finding is the steep increase in the concomitant prescription of levodopa with quetiapine after its introduction in 2000, so that in 2008 a remarkable 45.9% of all psychiatric patients with levodopa treatment also received quetiapine. Comparing patients with dopaminergic levodopa monotherapy vs. those with at least one more dopaminergic drug and therefore a likely underyling diagnosis of PD or Parkinson syndrome, the latter group had a moderately higher proportion of concomitant quetiapine use (25.5% vs. 18.7%, p=0.03), whereas the overall use of antipsychotics was similar (59.0% vs. 59.8%, p>0.05). We also found a noticeable temporal relationship between the introduction of quetiapine and the reduced use of

olanzapine plus levodopa that occurred from 2002 onwards. The combined use of other antipsychotics with levodopa did not show obvious time trends and was lower, with an average prevalence between 0.1 and 5.9% (see Table 4). Furthermore, we also identified seven patients where levodopa was combined with the formally contraindicated antidopaminergic drug metoclopramide.

DISCUSSION

Coprescription of antipsychotics has a high prevalence in psychiatric patients treated with levodopa, but counteracting pharmacodynamic effects on the dopamine system may represent a therapeutic challenge, independent of the underlying indication for levodopa. This observational study analyzed the long-term changes in prescribing behavior of combined use of levodopa and antipsychotics in a representative natural psychiatric inpatient setting.

Current strategies in order to control psychosis in the presence of PD and RLS include either a reduction or change of dopaminergic treatment because it can exacerbate hallucinations and other psychotic symptoms [2]. If psychotic symptoms persist even with the lowest levodopa dose that allows adequate control of motor symptoms additional treatment with antipsychotics is warranted. However, levodopa and most antipsychotics have antagonistic effects on the dopamine system, which may compromise levodopa's desired effects on motor function. Therefore antipsychotics with a low potential to induce EPS are required, and for a long time clozapine was the neuroleptic that met this requirement best [12].

Accordingly our results show that up to the introduction of olanzapine in 1997 clozapine was the most commonly coprescribed neuroleptic with levodopa. Clozapine has a regional selectivity for dopamine receptors in the mesolimbic „behavioral"

system, rather than the nigrostriatal „motor“ system, and over 80% of patients with PD respond to clozapine with complete or partial resolution of psychosis [12, 13]. Despite clozapine’s efficacy even at very low doses for this indication, adverse effects such as sedation, hypersalivation, orthostatic hypotension, and agranulocytosis are important limiting factors for its use, and the latter mandates frequent blood testing in patients treated with clozapine. In addition, several reports of fatal myocarditis in patients treated with clozapine were published between 1995 and 2000 [14-16]. Those reports and the introduction of alternative atypical antipsychotics coincide with the decreased concomitant use of clozapine with levodopa that we observed in our study, particularly after the introduction of olanzapine. Our data show that the combined prescription of olanzapine with levodopa first rapidly increased, but then equally rapidly decreased after the introduction of quetiapine. Although initial open-label studies of olanzapine showed beneficial effects [17, 18], later controlled trials showed no clear benefit and worsening of motor function, which argue against combined use of olanzapine with levodopa [19, 20].

In contrast, the combined use of levodopa with quetiapine is supported by several studies. Although two double-blind placebo-controlled studies failed to show beneficial effects of quetiapine on psychotic symptoms in PD [21, 22], an open-label as well as a recent well-designed double-blind controlled study between clozapine and quetiapine support the efficacy of quetiapine for the treatment of psychosis in PD [23, 24]. Indeed, based on our finding that in 2008 every other psychiatric patient with levodopa also received quetiapine, clinical prescribing practice also appears to be in accordance with a favorable efficacy and safety profile. Furthermore, a beneficial sleep-promoting effect has also been reported for quetiapine [2].

Melperone may be another alternative according to one uncontrolled study [25], which may explain the occasional combined use with levodopa in our data, but there are no controlled studies that support its use in the treatment of psychosis in PD. Other atypical antipsychotics are not commonly combined with levodopa according to our findings. Indeed, although drugs such as risperidone, aripiprazole or ziprasidone are generally considered to have a low risk to induce EPS, a worsening of motor function has been observed, particularly in the treatment of psychosis in PD patients, and their combined use with levodopa can therefore not be recommended [26-30]. Limitations of our descriptive study include particularly a lack of information on drug doses and clinical outcomes. The risk of levodopa-associated psychosis is dose-dependent [1], and patients with PD may receive daily doses of up to 1500 mg, whereas daily doses in RLS usully do not exceed 250 mg. This may also be a possible explanation for the observed higher proportion of concomitant quetiapine use in patients with several dopaminergic drugs. These patients may have a high risk of drug-induced psychosis on the one hand, but a high need to control motor symptoms without interference by antipsychotic treatment on the on the other hand. Antipsychotics are therefore typically started with very low doses in this situation, e.g. only 25 mg per day for quetiapine. Furthermore, although beyond the scope of our study's mainly descriptive aims and conclusions that focus on drug utilization over time, reliable information on the indication for levodopa and also antipsychotic drug use including quetiapine would have been of interest. Nevertheless, our findings provide important and valid information on the prevalence of levodopa use and its combination with antipsychotics in a very large psychiatric inpatient population. These data reflect the transfer of data from clinical trials and guidelines into daily prescribing behavior, and sometimes the experiences of prescribing physicians who

evaluate risks and benefits of pharmacotherapy in clinical practice may even anticipate recommendations based on controlled clinical trials.

In conclusion, quetiapine has now replaced clozapine as the most frequently coprescribed neuroleptic in psychiatric patients with levodopa therapy in clinical practice. This observation is in line with recent data from controlled studies that showed an overall favorable efficacy and safety profile of quetiapine in combination with levodopa. Clozapine use is supported by its well documented efficacy, but adverse effects, mainly bone marrow toxicity, are an important limiting factor for its use. Other antipsychotics than quetiapine and clozapine are less frequently combined with levodopa and with questionable rationale. Their use is generally not supported by appropriate evidence and should be discouraged unless exceptionally justifiable in individual patients.

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REFERENCES

1 Forsaa EB, Larsen JP, Wentzel-Larsen T, Goetz CG, Stebbins GT, Aarsland D, Alves G (2010) A 12-year population-based study of psychosis in Parkinson disease. Arch Neurol 67 (8): 996-1001

2 Diederich NJ, Fenelon G, Stebbins G, Goetz CG (2009) Hallucinations in Parkinson disease. Nat Rev Neurol 5 (6): 331-342

3 Schwab RS, Fabing HD, Prichard JS (1951) Psychiatric symptoms and syndromes in Parkinson's disease. Am J Psychiatry 107 (12): 901-907

4 Fenelon G, Goetz CG, Karenberg A (2006) Hallucinations in Parkinson disease in the prelevodopa era. Neurology 66 (1): 93-98

5 Moskovitz C, Moses H, 3rd, Klawans HL (1978) Levodopa-induced psychosis: a kindling phenomenon. Am J Psychiatry 135 (6): 669-675

6 Aarsland D, Larsen JP, Cummins JL, Laake K (1999) Prevalence and clinical correlates of psychotic symptoms in Parkinson disease: a community-based study. Arch Neurol 56 (5): 595-601

7 Turjanski N, Lees AJ, Brooks DJ (1999) Striatal dopaminergic function in restless legs syndrome: 18F-dopa and 11C-raclopride PET studies. Neurology 52 (5): 932-937

8 Stoner SC, Dahmen MM, Makos M, Lea JW, Carver LJ, Rasu RS (2009) An exploratory retrospective evaluation of ropinirole-associated psychotic symptoms in an outpatient population treated for restless legs syndrome or Parkinson's disease. Ann Pharmacother 43 (9): 1426-1432

9 Haueis P, Greil W, Huber M, Grohmann R, Kullak-Ublick GA, Russmann S (2011) Evaluation of drug interactions in a large sample of psychiatric inpatients: a data interface for mass analysis with clinical decision support software. Clin Pharmacol Ther 90 (4): 588-596

10 Grohmann R, Engel RR, Ruther E, Hippius H (2004) The AMSP drug safety program: methods and global results. Pharmacopsychiatry 37 Suppl 1: S4-11

11 Engel RR, Grohmann R, Ruther E, Hippius H (2004) Research methods in drug surveillance. Pharmacopsychiatry 37 Suppl 1: S12-15

12 The Parkinson Study Group (1999) Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease.. N Engl J Med 340 (10): 757-763

13 Pollak P, Tison F, Rascol O, Destee A, Pere JJ, Senard JM, Durif F, Bourdeix I (2004) Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up. J Neurol Neurosurg Psychiatry 75 (5): 689-695

14 Kilian JG, Kerr K, Lawrence C, Celermajer DS (1999) Myocarditis and cardiomyopathy associated with clozapine. Lancet 354 (9193): 1841-1845

15 Degner D, Bleich S, Grohmann R, Bandelow B, Ruther E (2000) Myocarditis associated with clozapine treatment. Aust N Z J Psychiatry 34 (5): 880

16 Bandelow B, Degner D, Kreusch U, Ruther E (1995) Myocarditis under therapy with clozapine. Schizophr Res 17 (3): 293-294

17 Wolters EC, Jansen EN, Tuynman-Qua HG, Bergmans PL (1996) Olanzapine in the treatment of dopaminomimetic psychosis in patients with Parkinson's disease. Neurology 47 (4): 1085-1087

18 Chacon JR, Duran E, Duran JA, Alvarez M (2002) [Usefulness of olanzapine in the levodopa-induced psychosis in patients with Parkinson's disease]. Neurologia 17 (1): 7-11

19 Breier A, Sutton VK, Feldman PD, Kadam DL, Ferchland I, Wright P, Friedman JH (2002) Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease. Biol Psychiatry 52 (5): 438-445

20 Goetz CG, Blasucci LM, Leurgans S, Pappert EJ (2000) Olanzapine and clozapine: comparative effects on motor function in hallucinating PD patients. Neurology 55 (6): 789-794

21 Ondo WG, Tintner R, Voung KD, Lai D, Ringholz G (2005) Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease. Mov Disord 20 (8): 958-963

22 Rabey JM, Prokhorov T, Miniovitz A, Dobronevsky E, Klein C (2007) Effect of quetiapine in psychotic Parkinson's disease patients: a double-blind labeled study of 3 months' duration. Mov Disord 22 (3): 313-318

23 Juncos JL, Roberts VJ, Evatt ML, Jewart RD, Wood CD, Potter LS, Jou HC, Yeung PP (2004) Quetiapine improves psychotic symptoms and cognition in Parkinson's disease. Mov Disord 19 (1): 29-35

24 Merims D, Balas M, Peretz C, Shabtai H, Giladi N (2006) Rater-blinded, prospective comparison: quetiapine versus clozapine for Parkinson's disease psychosis. Clin Neuropharmacol 29 (6): 331-337

25 Barbato L, Monge A, Stocchi F, Nordera G (1996) Melperone in the treatment of iatrogenic psychosis in Parkinson's disease. Funct Neurol 11 (4): 201-207

26 Ellis T, Cudkowicz ME, Sexton PM, Growdon JH (2000) Clozapine and risperidone treatment of psychosis in Parkinson's disease. J Neuropsychiatry Clin Neurosci 12 (3): 364-369

27 Factor SA, Molho ES, Friedman JH (2002) Risperidone and Parkinson's disease. Mov Disord 17 (1): 221-222

28 Friedman JH, Factor SA (2000) Atypical antipsychotics in the treatment of drug-induced psychosis in Parkinson's disease. Mov Disord 15 (2): 201-211

29 Fernandez HH, Trieschmann ME, Friedman JH (2004) Aripiprazole for drug-induced psychosis in Parkinson disease: preliminary experience. Clin Neuropharmacol 27 (1): 4-5

30 Schindehutte J, Trenkwalder C (2007) Treatment of drug-induced psychosis in Parkinson's disease with ziprasidone can induce severe dose-dependent off-periods and pathological laughing. Clin Neurol Neurosurg 109 (2): 188-191

TABLES

Tables

Table 1 - Characteristics of patients with levodopa therapy (N = 886).

Characteristics	Frequency
Age in years, median (range)	72 (12 - 95)
Gender, n (%)	
Female	515 (58.1)
Male	371 (41.9)
Primary ICD-10 diagnoses, n (%)	
Mental and behavioral disorders	838 (94.6)
Mood affective disorders	323 (36.5)
Organic psychoses	318 (35.9)
Schizophrenia	94 (10.6)
Neuroses	47 (5.3)
Psychoactive substance abuse	35 (4.0)
Personality and behavioral disorders	21 (2.4)
Unspecified	25 (2.8)
Other non-psychiatric diagnoses	23 (2.6)

Table 2 - Most frequent coprescribed drug classes in patients with levodopa therapy

	n	%
Levodopa	**886**	**100**
Coprescribed drug classes		
Antipsychotics	528	59.6
Antidepressants	526	59.4
Anxiolytics, sedatives and hypnotics	347	39.2
NSAIDs	222	25.1
Diuretics	219	24.7
Drugs for peptic ulcer	219	24.7
Renin-angiotensin-aldosterone system inhibitors	183	20.7
Anticonvulsants	178	20.1
Laxatives	169	19.1
Beta-blocking agents	143	16.1
Other hormones	138	15.6
Antithrombotics	129	14.6
Mineral supplements	128	14.4
Anti-dementia agents	106	12.0
Antianemic agents	94	10.6
Vitamins	76	8.6
Calcium channel blockers	75	8.5
Cardiac stimulants and antiarrhythmics	66	7.4
Antidiabetic agents	65	7.3

Table 3 - Coprescription of other dopaminergic drugs with levodopa

	n	%
Levodopa	**886**	**100**
Coprescribed other dopaminergic drugs		
At least one dopaminergic drug listed below	239	27.0
Amantadin	64	7.2
Pramipexol	44	5.0
Selegilin	36	4.1
Entacapon	36	4.1
Cabergolin	29	3.3
Ropinirol	24	2.7
Pergolid	21	2.4
Bromocriptin	14	1.6
Dihydroergocriptin	12	1.4
Lisurid	9	1.0
Tolcapon	2	0.2
Apomorphin	1	0.1
Rotigotin	1	0.1
Quinagolid	0	0
Rasagilin	0	0

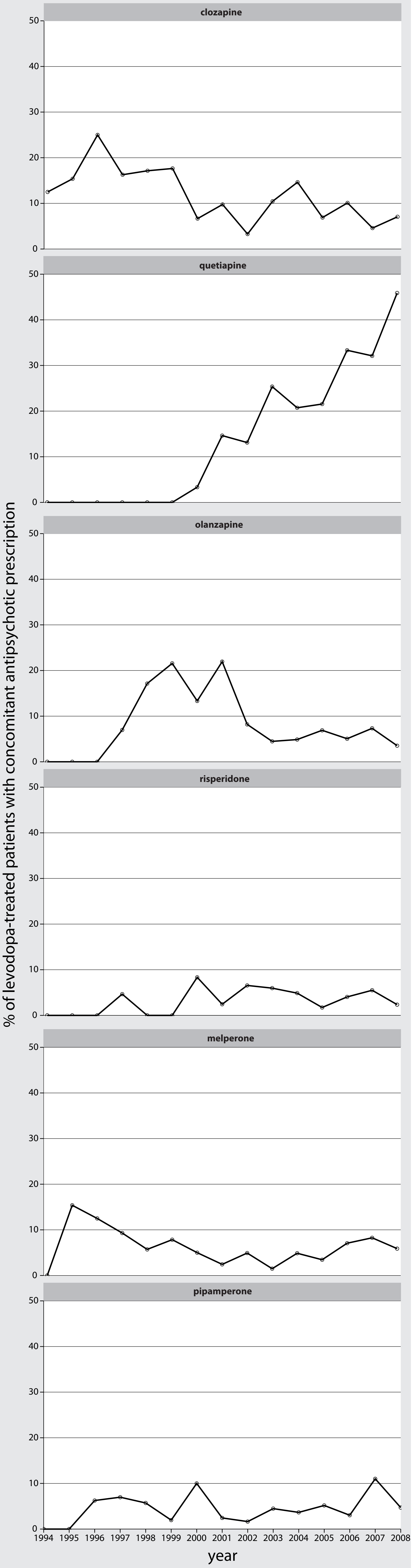
Table 4 - Coprescription of antipsychotics with levodopa including time trends

	Overall frequency		Time trends		
			1994-2002 (n=328)	2003-2008 (n=558)	
	n	%	%	%	p-value[1]
Levodopa	**886**	**100**	**100**	**100**	**-**
Coprescribed antipsychotics					
Atypical					
Quetiapine	182	20.5	4.9	29.7	<0.001
Clozapine	87	9.8	11.9	8.6	0.11[2]
Olanzapine	73	8.2	12.8	5.6	<0.001
Risperidone	34	3.8	3.7	3.9	0.83
Amisulpride	14	1.6	0.6	2.2	0.08
Aripiprazole	3	0.3	0.5	0	0.18
Zotepine	3	0.3	0.6	0.2	0.29
Sulpiride	2	0.2	0	0.4	0.28
Sertindole	1	0.1	0	0.2	0.44
Ziprasidone	1	0.1	0	0.2	0.44
Conventional					
Melperone	52	5.9	6.4	5.6	0.60
Pipamperone	46	5.2	4.6	5.6	0.52
Chlorprothixene	24	2.7	2.1	3.0	0.42
Prothipendyle	23	2.6	2.1	2.9	0.51
Haloperidol	19	2.1	1.8	2.3	0.62
Levomepromazin	14	1.6	2.4	1.1	0.12
Flupentixole	9	1.0	0	1.6	0.02
Perazine	7	0.8	1.8	0.2	0.007
Metoclopramide	7	0.8	0.9	0.7	0.75

[1] chi-square test comparing time strata 1994-2002 vs. 2003-2008

[2] 1994-1999 (before introduction of quetiapine) vs. 2000-2008: 17.5% vs. 8.1%, p<0.001

Figure 1


clozapine
quetiapine
olanzapine
risperidone
melperone
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% of levodopa-treated patients with concomitant antipsychotic prescription
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